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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,596	11/21/2001	Jeffrey M. Drazen	0092662-0032	3876

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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,596	DRAZEN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed December 20, 2002. Applicants arguments presented in the response of December 20, 2002 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Green (American Journal of Respiratory Cell and Molecular Biology (1995) 13:25-33).

Green teaches methods for detecting B_2AR genotypes wherein the methods comprise performing PCR using two sets of primers wherein the first set of primers contains a primer which specifically hybridizes to a portion of the B_2AR gene comprising a sequence encoding an Arg at residue 16 and wherein the second set of primers contains a primer which specifically hybridizes to a portion of the B_2AR gene comprising a sequence encoding a Gly at residue 16 (see Table 1; page 26, col. 2 and page 29-30). Each primer set amplifies a portion of the B_2AR gene comprising the sequence encoding amino acid residue 16. Green further teaches that PCR is performed using standard PCR reagents including buffers, DNA polymerase and dNTPs (page 26) and that the assays were performed using control polynucleotides encoding either the Arg16 or

Gly16 variant. Accordingly, the method of Green requires a container comprising a primer set which amplifies a portion of the B_2AR gene including the nucleotide sequence encoding amino acid residue 16, a buffer, a DNA polymerase and dNTPs and containers comprising said primer set, a buffer, DNA polymerase, dNTP and control polynucleotides. It is noted that while the claims require a kit and require that the primer set and reagents are arranged together in a container, the claims do not recite any positive limitations that distinguish the claimed kits over the containers comprising the reagents set forth by Green. It is further noted that kits are considered to be simply parts capable of being assembled (*In re Venezia*, 530 F. 2d 956, USPQ 149 (CCPA 1976)) and that the recitation of the term "kit" does not impart any specific structural limitations or arrangement of parts/items.

3. Claims 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Reihsaus (American J. Resp. Cell Molec Biol. 1993. 83:334-339).

Reihsaus discloses methods for detecting the presence of polymorphisms in the B_2 -adrenergic receptor gene and in particular teaches methods which detect the presence of the Gly16 and Arg16 variants of the B_2 -adrenergic receptor gene. Reihsaus teaches that the Gly16 genotype is more prevalent in severe forms of asthma than the Arg16 genotype. In the methods of Reihsaus, polymorphisms in the B_2AR gene are detected by first amplifying sample DNA using a primer set which amplifies a portion of the B_2AR gene including sequences which encode for the Arg16 and Gly16 variants and then determining the sequence of the amplified DNA. PCR amplification was performed using conventional reagents, which are known to include dNTPs,

buffer, and a DNA polymerase (Taq polymerase herein; see page 335). Accordingly, the method of Reihsaus requires a container comprising a primer set which amplifies a portion of the B_2AR gene that includes the nucleotide sequence encoding amino acid residue 16, a buffer, a DNA polymerase and dNTPs. It is noted that while the claims require a kit and require that the primer set and reagents are arranged together in a container, the claims do not recite any positive limitations that distinguish the claimed kits over the containers comprising the reagents set forth by Green. It is further noted that kits are considered to be simply parts capable of being assembled (*In re Venezia*, 530 F. 2d 956, USPQ 149 (CCPA 1976)) and that the recitation of the term "kit" does not impart any specific structural limitations or arrangement of parts/items.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green (American Journal of Respiratory Cell and Molecular Biology (1995) 13:25-33) in view of the Stratagene Catalog (1988, page 39).

It is noted that this rejection applies to the claims based on the interpretation that the term "kit" may be given patentable weight.

Green teaches methods for detecting B_2AR genotypes wherein the methods comprise performing PCR using two sets of primers wherein the first set of primers contains a primer which specifically hybridizes to a portion of the B_2AR gene comprising a sequence encoding an Arg at residue 16 and wherein the second set of primers contains a primer which specifically hybridizes to a portion of the B_2AR gene comprising a sequence encoding a Gly at residue 16 (see Table 1; page 26, col. 2 and page 29-30). Each primer set amplifies a portion of the B_2AR gene comprising the sequence encoding amino acid residue 16. Green further teaches that PCR is performed using standard PCR reagents including buffers, dNTPs, and DNA polymerase (page 26) and that the assays were performed using control polynucleotides encoding either the Arg16 or Gly16 variant. Green (page 32) teaches that the Gly16 polymorphism is associated with the nocturnal asthmatic phenotype and states that given the prevalence of the Gly16 polymorphism in the asthmatic population, this "B_2AR genotype has the potential to be an important factor in modifying bronchial hyperactivity, affecting the severity of the disease or defining certain asthmatic phenotypes". Green does not teach packaging the B_2AR allele specific primer sets, reagents for performing PCR and control polynucleotides in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the B_2AR allele specific primer sets, reagents for performing PCR (buffers, dNTPs, and DNA polymerase) and control polynucleotides in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to determine the genotype of the B_2AR gene with respect to the Arg16Gly polymorphism.

5. Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reihsaus (American J. Resp. Cell Molec Biol. 1993. 83:334-339) in view of the Stratagene Catalog (1988, page 39).

It is noted that this rejection applies to the claims based on the interpretation that the term "kit" may be given patentable weight.

Reihsaus discloses methods for detecting the presence of polymorphisms in the B_2 -adrenergic receptor gene and in particular teaches methods which detect the presence of the Gly16 and Arg16 variants of the B_2 -adrenergic receptor gene. Reihsaus teaches that the Gly16 genotype is more prevalent in severe forms of asthma than the Arg16 genotype. In the methods of Reihsaus, polymorphisms in the B_2AR gene are detected by first amplifying sample DNA using

primers which amplify a portion of the B_2AR gene including sequences which encode for the Arg16 and Gly16 variants and then determining the sequence of the amplified DNA. The methods of Reihsaus utilize the following reagents: primers for amplifying a portion of the B_2AR gene including sequences encoding residue 16, sequencing primers, DNA polymerase, dNTPs, ddNTPs, and buffers (see page 335). Reihsaus (page 338) teaches that patients with the Arg16 to Gly polymorphism were more likely to be steroid dependent and to require immunization therapy. Reihsaus also states that this polymorphism "may be associated with a different clinical status, suggesting that an alteration in the gene encoding for the B_2AR gene plays an accessory role in the pathogenesis of asthma in certain patients" (see abstract). Reihsaus does not teach packaging the reagents required to amplify and determine the sequence of the B_2AR gene in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primer set for amplifying B_2AR sequences including sequences encoding residue 16, reagents required to perform PCR(amplification buffers, dNTPs, DNA polymerase) and primers and reagents required to perform sequencing reactions (e.g., sequencing primers, sequencing buffers, dNTPs, ddNTPs, DNA polymerase) in a kit for the

expected benefits of convenience and cost-effectiveness for practioners in the art wishing to determine the genotype of the B_2AR gene with respect to the Arg16Gly polymorphism.

6. **RESPONSE TO ARGUMENTS**

In the response filed December 20, 2002, Applicants traversed each of the above rejections together for the reasons that follow. Applicants state that the claims are drawn to a kit "which is a single container in which are contained primers appropriate and sufficient for amplification of the recited polymorphisms. Nowhere does Green teach a container housing such selected primers." However, the term "kit" is not defined in the specification and there is no specific art recognized definition for this term which requires that a kit is limited to a special housing that contains a set of reagents. As stated in *In re Venezia*, 530 F. 2d 956, USPQ 149 (CCPA 1976), kits are considered to be simply parts capable of being assembled and the recitation of the term "kit" does not impart any specific structural limitations or arrangement of parts/items.

Applicants further argue that Green does not provide the motivation to package primers in a kit. It is argued that a p value of less than 0.001 is required before one of ordinary skill in the art would be motivated to produce a kit. Applicants contend that while a p value of less than 0.05 is meaningful in a research context, it is not a standard for a diagnostic test. This argument is not convincing because the claims are drawn to a kit and not to a diagnostic test. There is no requirement in the art that a kit is generated only if the primers can be used in a diagnostic test and in particular there are no teachings in the art that a kit is generated only if the components of

the kit can be used in a diagnostic test that generates a p value of 0.001. While Applicants may choose to only manufacture a kit if the kit is useful in a method that generates a p value of less than 0.0001, this is not the standard in the art. Applicants contend that the data generated by Reihsaus was preliminary and that there is no reasonable expectation of success in generating a kit. This argument is not convincing because whether a kit proves to be financially or commercially successful is not the basis by which to determine a "reasonable expectation of success". One of skill in the art would have more than a reasonable expectation of success of, for example, taking a tube containing primers and placing the tube in a box to generate "a kit". Applicants state that the cited art provides at most a disclosure which would motivate a researcher in the field to try to find a correlation that would support the production of a kit. However, Applicants are applying a standard for generating kits which is far beyond that which is applied in the art. Applicants have not provided any case law to support their conclusion that kits are generated only for those components that can be used in a diagnostic test with a p value of 0.001. As discussed above, the motivation to arrive at the claimed invention need not be the same as that proposed by Applicants. Green provides the motivation to combine the Arg16 and Gly16 B_2AR allele specific primers in a kit because Green teaches that these primers are useful for determining the genotype of patients. Reihsaus provides the motivation to combine the primers for amplifying the Arg16 and Gly16 B_2AR sequences in a kit because Reihsaus teaches that these primers are useful for determining the genotype of patients and can be used to further study the relationship between the Arg/Gly16 polymorphism and use of corticosteroids and the accessory

role this polymorphism may play in the pathogenesis of asthma. Therefore, it is maintained that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primer set for amplifying the B_2AR Arg16 and Gly16 alleles in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to determine the genotype of the B_2AR gene.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 10, 2003